REMARKS

Claims 1, 3, 7-10, 18, 32-38, 40, and 41, as amended, appear in this application for the Examiner's review and consideration. Claims 2, 4-6, 11-17, and 39 have been cancelled. Claims 19-31 have been withdrawn by the examiner as directed to non-elected subject matter. The claims have been amended to more particularly point out the claimed subject matter and to correct inadvertent minor spelling and editorial errors, but no new matter has been added.

Claims 1-3, 7-10, 18, and 32-41 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious over Japanese Patent 09-249562 to Nobuko *et al.* (JP '562), in view of U.S. Patent No. 6,569,463 to Patel *et al.*, (the '463 patent) and further in view of U.S. Patent No. 4,150,113 to Hoogendoorn *et al.* (the '113 patent), for the reasons set forth on pages 2-5 of the Office Action. Applicants respectfully traverse.

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that claimed subject matter should be carried out and would have a reasonable likelihood of success. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). As the Examiner is well aware, in order to form a proper basis for a rejection under 35 U.S.C. § 103, the prior art must provide some suggestion, either explicit or implicit, of the combination that allegedly renders a claimed invention obvious. *M.P.E.P.*, § 2142 (June 1998), *see also, Panduit Corp. v. Denisson Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir. 1987). The Examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Sang Su Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); citing *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The need for specificity is paramount, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. *Id.* The Examiner's conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority. *Id.*

The claims recite a method of treating muscle spasms comprising administering an effective anti-spasmodic amount of tizanidine, an acidulant in an amount to obtain saliva with a pH of 2 to 7, a disintegrant selected from the group consisting of crospovidone and microcrystalline cellulose, and a pharmaceutically acceptable excipient which are formulated into a fast dissolving tablet, where 80% or more of the tizanidine in the tablet is released within 20 minutes after administration of the drug. Further the tizanidine is administered buccally or sublingually so that the tizanidine is absorbed through the mucosa lining of the mouth; and the tizanidine bioavailability AUC_{inf} is increased by 10% or more as compared to the AUC_{inf} of an immediate release tizanidine enteral dosage form absorbed through the gastro-intestinal track having an equivalent dose of tizanidine.

In contrast, JP '562 purportedly discloses a tizanidine hydrochloride preparation obtained by adequately compounding tizanidine hydrochloride with commonly used additives such as a vehicle, a lubricant, a flavoring agent, a binder and a disintegrant and formulation the resultant mixture into tablets, capsules, granules, powder, etc. (JP '562 abstract). In the formulation process, the pH of the preparation is adjusted to <=5.5, preferably in the range of 5.4-2.2 by adding an organic acid such as citric acid or tartaric acid or an inorganic acid such as sodium dihydrogenphosphate as an acidic additive. (*Id.*)

Contrary to the very limited discussion within the Office Action, the '463 patent is directed to pharmaceutical delivery systems for pharmaceutically active ingredients where the active is in a rapid dissolvable and more solubilized state, the composition includes a solid carrier, the solid carrier including a substrate and an encapsulation coat on the substrate. (The '463 patent, col. 2, ll. 17-19 and col. 3, ll. 61-66). One object of the invention is to provide solid pharmaceutical compositions of coated substrate materials without the need for binders and another object is to provide solid pharmaceuticals having better protection of the upper gastrointestinal tract from effects of the active ingredient. (*Id.* at ll. 30-32 and 40-44). The active ingredient can be hydrophilic, lipophilic, amphiphilic or hydrophobic, and can be solubilized, dispersed, or partially solubilized and dispersed, in the encapsulation coating. (*Id.* col. 4, ll. 28-32). After disclosing 52 categories of active ingredients and 199 different active pharmaceutical ingredients, tizanidine is mentioned once, thereafter, it is one of 54 most preferred ingredients. (*Id.* col. 4, l. 53 to col. 7, l. 15).

The '113 patent purportedly discloses a novel dentifrice containing **glucose oxidase as its essential active ingredient**. (The '113 patent, col. 1, ll. 15-16, emphasis added). The action of the enzyme in the dentifrice is twofold: (1) the formation of hydrogen peroxide (formed by the oxidative decomposition of glucose) tends to normalize mouth flora and (2) it facilitates the loosening and removal of plaque on the teeth. (*Id.* ll. 19-25). Food in the mouth will decrease the pH level, which dependent upon the nature of the material may decrease the pH to value of 5.5 to 4.5 and sometimes even lower. (*Id.* at col. 2, ll. 1-3). The zone below 5.5 is often called the danger zone because under such conditions the calcium compounds of the tooth will dissolve in the saliva leading to decay of the tooth. (*Id.* at col. 2, ll. 3-7). To solve this problem of low acidity, the enzyme glucose oxidase was added to a dentifrice. (*Id.* ll. 41-49).

JP '562 fails to render obvious the claims as it does not suggest a method of treating muscle spasms by administering a rapidly dissolving tablet which dissolves in the mouth. The Office attempts to remedy this deficiency by coupling the '463 patent with JP '562, but this is unavailing as the '463 patent teaches a solid pharmaceutical composition for the delivery of a wide variety of pharmaceutical ingredients using a solid carrier which includes a substrate and an encapsulation coat on the substrate, neither of which suggest the method of treatment using a rapidly dissolving tablet as recited in the claims. The focus of the '463 patent is on the delivery system (requiring encapsulation) and not on the active pharmaceutical ingredient, this is clear from the enumeration of a never-ending list of drugs which runs from column 4 line 22 to column 9, line 60, that is a list of active ingredients that is over five columns long.

The Office attempts to portray the '463 patent out of context and focuses on tizanidine (one of 199 listed drugs) while ignoring the main focus of the patent: the excipient combination that is necessary to achieve the delivery method. The '463 patent needs a particular excipient and its encapsulation to achieve the generally desired properties. What the Office proposes requires the skilled artisan to ignore this teaching, yet neither the JP 562 nor the '463 patent teach this exclusion. The only method by which a skilled artisan would know to ignore the main teaching of the '463 patent is if the skilled artisan had the benefit of the present claims. In other words, the rejection is merely a mosaic rejection composed by

using the applicant's claims as a blueprint. This piecemeal analysis is clearly demonstrated by the Office's use of the '113 patent in the rejection.

The '113 patent is directed to dentifrice containing an enzyme, which is a non-analogous subject matter to the method of treating muscle spasms. The Office attempts to use this reference to achieve the pH range of the claim, however the '113 patent teaches against such range. The reference states that a pH value of 5.5 to 4.5 is achieved during eating and that the zone below 5.5 is often called the danger zone because it leads to tooth decay. Thus, the reference teaches to use the enzyme glucose oxidase to **increase** the pH level and not lower it as recited in the claim. In fact, the enzyme glucose oxidase works against the acidulant of the claim.

The above paragraph is just another example of the piecemeal analysis in this rejection. After establishing tizanidine compositions the Office cites the '463 patent for buccal compositions, but ignores the need for a particular excipient and encapsulation, then the Office cites to the '113 patent to achieve the pH range, but then also ignores that it relates to a dentifrice with an enzyme to increase the pH. The combination of references requires the hindsight analysis so often cautioned against and which cannot establish obviousness of the claims. The rejection cannot stand because the analysis lacks the fundamental reasoning as to why the skilled artisan would combine such references (absent the teaching of the claims) and whether the skilled artisan would have a reasonable expectation of success (even when he must ignore the explicit teachings of the claims).

Accordingly, the rejection of claims 1-3, 7-10, 18, and 32-41 under 35 U.S.C. § 103(a) as rendered obvious by JP '562 in view of the '463 patent and further in view of the '113 patent cannot stand and should be withdrawn.

Accordingly, it is believed that claims 1-3, 7-10, 18, and 32-41 are now in condition for allowance, early notice of which would be appreciated.

If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 10-0600.

Respectfully submitted,

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By: _____
Craig L. Puckett (Reg. No. 43,023)

Kenyon & Kenyon LLP
Intellectual Property Department
1500 K Street NW
Washington, DC 20005
(202) 220-4200